BASIC RESEARCH

Remote ischaemic preconditioning protects against cardiopulmonary bypass-induced tissue injury: a preclinical study

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Objectives: To test the hypothesis that remote ischaemic preconditioning (rIPC) reduces injury after cardiopulmonary bypass (CPB).
Design: Randomised study with an experimental model of CPB (3 h CPB with 2 h of cardioplegic arrest). Twelve 15 kg pigs were randomly assigned to control or rIPC before CPB and followed up for 6 h.
Intervention: rIPC was induced by four 5 min cycles of lower limb ischaemia before CPB.
Main outcome measures: Troponin I, glial protein S-100B, lactate concentrations, load-independent indices (conductance catheter) of systolic and diastolic function, and pulmonary resistance and compliance were measured before and for 6 h after CPB.
Results: Troponin I increased after CPB in both groups but during reperfusion the rIPC group had lower concentrations than controls (mean area under the curve −57.3 (SEM 7.3) *v* 89.0 (11.6) ng·h/ml, p = 0.02). Lactate increased after CPB in both groups but during reperfusion the control group had significantly more prolonged hyperlactataemia (p = 0.04). S-100B did not differ between groups. Indices of ventricular function did not differ. There was a tendency to improved lung compliance (p = 0.07), and pulmonary resistance changed less in the rIPC than in the control group during reperfusion (p = 0.02). Subsequently, peak inspiratory pressure was lower (p = 0.001).
Conclusion: rIPC significantly attenuated clinically relevant markers of myocardial and pulmonary injury after CPB. Transient limb ischaemia as an rIPC stimulus has potentially important clinical applications.

Cardiopulmonary bypass (CPB) remains an essential element of the surgical correction of most congenital and many acquired cardiac lesions. Despite significant advances in the technique, CPB is still complicated by multisystem injury, the mechanisms of which include ischaemia–reperfusion (IR) injury and a detrimental systemic inflammatory response.[1] Cardiac, pulmonary and neuronal injury and dysfunction remain important clinical problems after CPB.[2]

Ischaemic preconditioning is a powerful protective strategy that attenuates IR injury. It is induced by exposing tissues to brief periods of ischaemia before a prolonged ischaemic insult: this procedure reduces infarction when the preconditioning stimulus is applied to the same tissue that undergoes infarction (local preconditioning) and has been studied in humans.[3] However, the preconditioning stimulus has systemic effects to protect distant tissues from subsequent ischaemia, and this variant is called remote ischaemic preconditioning (rIPC). We have already reported a protective effect induced by transient limb ischaemia in experimental myocardial infarction.[4] Limb ischaemia to induce rIPC has potential implications in a variety of clinical IR syndromes and may be easier to induce than local preconditioning. In this preclinical study we tested the hypothesis that rIPC attenuates cardiac, pulmonary and neuronal injury induced by CPB.

METHODS

Animals and study design

Twelve 15 kg Yorkshire pigs were randomly assigned to receive either rIPC or a sham procedure (control) immediately before CPB (see below). The protocol was approved by the Institutional Animal Care and Use Committee of the research institute in the Hospital for Sick Children, and experiments were conducted in compliance with institutional guidelines.

Surgery and CPB

Animals were pretreated with intramuscular ketamine (33 mg/kg) and midazolam (1 mg/kg). Anaesthesia was induced with inhaled isoflurane (5%). After the onset of anaesthesia, the trachea was intubated. Muscle relaxation was obtained with peripheral intravenous infusion of pancuronium. Ventilation was controlled with a Servo 900C ventilator (Siemens Medical Systems, Solna, Sweden). Anaesthesia was maintained with isoflurane 2%. Oxygenation, electrolytes and ventilation were maintained at physiological levels by hourly blood gas measurements. The right and left carotid arteries and internal jugular veins were cannulated, and suprapubic bladder catheterisation was performed. A thermodilution pulmonary artery catheter and atrial septal sizing balloon (positioned in the inferior vena cava) were inserted through the internal jugular veins. A conductance catheter (5 French; Millar Instruments, Houston, Texas, USA) was inserted retrogradely from the right carotid artery into the left ventricular apex under fluoroscopic control.

Abbreviations: $avDO_2$, arteriovenous oxygen content difference; CPB, cardiopulmonary bypass; DC, direct current; Fextr, extrapolated maximum flow at the beginning of the exhalation; IR, ischaemia–reperfusion; Poccl, pressure signal during occlusion; PVR, pulmonary vascular resistance; rIPC, remote ischaemic preconditioning; Vextr, extrapolated exhaled volume; VO_2, oxygen consumption

After median sternotomy and heparinisation (unfractionated heparin to achieve a target activated clotting time $>$ 480 s), the pericardium was opened and the heart exposed. During this time rIPC was induced as described below.

Atrial pacing wires were attached and baseline recordings were made at a heart rate of 120 beats/min. Animals were then established on CPB with a standard clinical circuit with right atrial (32F-24 cannula; Stockert Instrument, Munich, Germany) and ascending aorta cannulation (14 French cannula; Jostra, Hirrlingen, Germany), a membrane oxygenator (Dideco702; Dideco, Mirandola, Italy) and a roller pump (100 ml/kg flow). Animals underwent a total of 180 min of CPB, including 120 min of aortic cross clamping and cardioplegic arrest, which was achieved with cold blood/crystalloid (2:1) cardioplegia infused into the aortic root as a single dose. The central temperature was maintained at 32℃ until 20 min before release of the aortic cross clamp. Cooling and warming were achieved by a heat exchanger. All hearts returned to ventricular fibrillation and were restored to sinus rhythm by internal direct current (DC) cardioversion.

Vital signs (blood pressure, heart rate, central venous pressure and rectal temperature), ventilator tidal volumes and pressures were monitored in the post-bypass period. Arterial samples for blood gas measurement were drawn hourly and ventilator settings were appropriately adjusted. Plasma potassium, ionised calcium and magnesium were maintained in the normal range with appropriate intravenous supplements. Whole blood was used as additional colloid to maintain the right atrial pressure at 5–10 cm H_2O. The goal was to avoid acidosis, to maintain a systolic arterial blood pressure, and to maintain adequate peripheral perfusion. Animals received dobutamine if systolic blood pressure fell by 30% of baseline values, cardiac output fell by 20% of baseline or there were other clinical features of inadequate tissue perfusion. Dose adjustments were permitted (2.5–10 μg/kg/min range) and, if necessary, epinephrine was administered. Haemodynamic status was assessed every 30 min. Ventricular fibrillation was treated with DC cardioversion.

Induction of rIPC

The rIPC stimulus was tourniquet occlusion of blood flow to one hind limb with four cycles of 5 min occlusion followed by 5 min reperfusion as previously described.[4] Circulatory arrest in the limb was confirmed by vascular Doppler.

Biochemical assessments

Serum was collected at baseline, on release of the aortic cross clamp, at the end of CPB and at 1, 3 and 6 h after CPB. Troponin I was measured with a commercially available sandwich immunoassay (Bayer, USA). Protein S-100 was measured with an immunoradiometric assay (Sangtec, Bromma, Sweden) and lactate measured by colorimetric assay (Vitros, USA).

Assessment of ventricular function

Real-time left ventricular pressure–volume loops were generated by using eight polar conductance catheters with an integrated micromanometer (5 French; Millar) as previously described.[5] Preload was varied by transient balloon occlusion of the inferior vena cava. Volume and pressure data were analysed offline by custom-designed software. Systolic and diastolic load-independent indices of left ventricular performance (slope of the end systolic pressure–volume relationship and slope of the end diastolic pressure–volume relationship) were measured at baseline and 1, 3 and 6 h after CPB at a heart rate of 120 beats/min.

Assessment of lung mechanics and pulmonary vascular resistance

Lung mechanics

Airflow and airway opening pressure were measured with a fixed-orifice pneumotachograph (Korr Medical Technologies, Salt Lake City, Utah, USA) inserted between the endotracheal tube and the ventilator Y piece. Changes in lung volume were calculated by integration of the flow signal by using software for dynamic measurements and by custom-built software for the analysis of the single occlusion technique in quasistatic measurement as described previously.[6] Flow and pressure signals were recorded by analogue to digital conversion at 250 Hz, and customised software was used for data acquisition and valve control. Dynamic compliance, resistance, tidal volume, minute ventilation and ventilatory pressure parameters were recorded at baseline and 1, 3 and 6 h after CPB during normal ventilation.

Static measurements were based on the principle of the single occlusion technique. During measurements, airways were occluded at the end inspiration for 300 ms. Static compliance and resistance were calculated from the pressure signal during occlusion (Poccl) and the flow signal during the following exhalation. The flow–volume curve of the exhalation was plotted and the time constant of the system was calculated as the slope of the flow–volume curve. Extrapolated values of exhaled volume (Vextr) and maximum flow at the beginning of the exhalation (Fextr) were calculated and the values of the static compliance and resistance were obtained (for compliance, Vextr/Poccl, and for resistance, Poccl/Fextr).

Pulmonary vascular resistance

Oxygen consumption ($\dot{V}o_2$ in ml/kg/min) was determined with a respiratory mass spectrometry mixed-expiration inert-gas dilution method as previously described.[7] Systemic and pulmonary arterial, right atrial and pulmonary arterial wedge pressures were measured, and blood samples were taken from the pulmonary and systemic arteries for measurements of partial pressures of oxygen and carbon dioxide and of haemoglobin saturation. The arteriovenous oxygen content difference ($avDo_2$ in ml/l) and cardiac output (by the Fick principle in $\dot{V}o_2/avDo_2$) were calculated. Indexed pulmonary vascular resistance (PVR) was derived from the transpulmonary pressure gradient by standard formula (PVR/m^2) and reported in Wood units (WU/m^2).

Calculations and statistics

All data are expressed as mean (SEM), unless otherwise stated. Each group was compared at 1, 3 and 6 h by Student's t test. Repeated measures analysis of variance was used to compare data between treatment groups to define any group–time interaction during the reperfusion period. We analysed data as between factor (treatment group) and within factor (time). As some of the control group animals died after 3 h, this group was analysed until the 3 h time point only. For this analysis data were adjusted for baseline values. This adjustment had no effect on analysis at individual time points. We assumed that the compound symmetry assumption was not violated. Data were also compared at individual time points. GraphPad Prism V.3.00 (GraphPad Software, San Diego, California, USA) was used for analysis. In all cases, $p < 0.05$ was considered significant.

RESULTS

All six animals in each group survived to 3 h. Two animals in the control group died between 3 and 6 h. All rIPC group animals survived to 6 h. Baseline haemodynamic variables did not differ between groups (table 1). Four animals in the control group and three in the rIPC group required inotrope

Table 1 Haemodynamic profile, systemic and pulmonary blood gases, ventilation parameters and PVR in control and rIPC groups at baseline and 1, 3 and 6 h after reperfusion

	Baseline			1 h			3 h			6 h		
	Control (n = 6)	rIPC (n = 6)	p Value	Control (n = 6)	rIPC (n = 6)	p Value	Control (n = 6)	rIPC (n = 6)	p Value	Control (n = 4)	rIPC (n = 6)	p Value
Mean pressures (mm Hg)												
BP	49.5 (1.7)	51.7 (2.5)	0.5	44.3 (3.0)	38.3 (2.9)	0.2	41.3 (3.2)	41.3 (3.2)	1.0	44.0 (4.4)	43.0 (3.4)	0.9
PA	17.8 (1.4)	17.5 (2.0)	0.9	21.0 (2.2)	20.3 (1.6)	0.8	23.3 (2.3)	20.0 (1.3)	0.2	21.8 (3.2)	23.0 (1.7)	0.7
LA	8.2 (1.1)	8.6 (0.6)	0.7	9.7 (1.1)	8.7 (0.8)	0.5	10.3 (1.0)	8.7 (0.3)	0.2	11.8 (1.7)	9.7 (0.8)	0.2
SBP	57.2 (2.9)	61.8 (1.7)	0.2	60.1 (4.4)	53.9 (3.1)	0.5	56.1 (3.2)	55.1 (3.8)	0.9	59.1 (6.2)	61.2 (2.7)	0.7
Systemic data												
Hb (g/dl)	9.3 (0.5)	9.4 (0.5)	0.8	10.6 (0.8)	10.9 (0.8)	0.8	12.0 (1.6)	11.8 (0.9)	0.9	13.0 (1.2)	12.8 (1.1)	0.9
P_{O_2} (mm Hg)	182.5 (14.5)	173.0 (8.1)	0.6	162.2 (18.4)	148.0 (13.0)	0.5	159.5 (25.6)	169.9 (30.2)	0.8	150.4 (31.6)	133.0 (5.9)	0.5
P_{CO_2} (mm Hg)	35.2 (1.4)	33.8 (0.7)	0.4	35.7 (1.7)	38.3 (2.3)	0.4	38.8 (2.6)	37.9 (2.1)	0.8	36.0 (2.5)	41.1 (1.6)	0.1
Saturation	99.3 (0.1)	99.3 (0.1)	0.9	98.9 (0.2)	98.7 (0.2)	0.5	97.8 (1.2)	98.9 (0.2)	0.4	96.7 (2.6)	98.4 (6.3)	0.4
BE	−5.4 (0.8)	−4.5 (0.5)	0.4	−7.1 (0.5)	−5.9 (1.5)	0.5	−7.5 (1.2)	−6.3 (1.3)	0.5	−4.3 (2.2)	−4.3 (1.4)	1.0
Pulmonary data												
P_{O_2} (mm Hg)	43.3 (2.6)	42.8 (1.3)	0.9	37.9 (3.9)	35.4 (2.1)	0.6	35.7 (3.0)	35.8 (4.6)	1.0	36.8 (3.4)	34.4 (6.1)	0.8
Saturation	74.5 (2.8)	75.7 (1.5)	0.7	63.1 (5.1)	59.2 (4.6)	0.6	59.7 (4.1)	58.4 (6.3)	0.9	62.6 (5.7)	54.2 (9.4)	0.5
$\dot{V}O_2$ (ml/min/kg)	5.4 (0.3)	5.2 (0.2)	0.5	5.2 (0.3)	5.0 (0.2)	0.6	5.4 (0.3)	4.8 (0.4)	0.3	5.2 (0.3)	5.0 (0.4)	0.8
Ventilation data												
PIP (cm H_2O)	16.9 (0.9)	14.6 (0.8)	0.1	21.7 (0.5)	18.8 (0.3)	0.001	22.2 (0.7)	19.4 (0.3)	0.002	21.3 (0.6)	21.3 (0.5)	1.0
PEEP (cm H_2O)	5.8 (0.3)	5.5 (0.4)	0.6	5.6 (0.4)	5.5 (0.4)	0.9	5.6 (0.4)	5.3 (0.5)	0.7	6.0 (0.5)	5.8 (0.6)	0.8
MAP (cm H_2O)	8.5 (0.3)	7.9 (0.4)	0.2	9.9 (0.5)	8.9 (0.2)	0.1	9.9 (0.5)	8.9 (0.3)	0.1	9.8 (0.8)	9.7 (0.5)	0.9
VT (ml)	180.3 (11.0)	179.8 (6.7)	1.0	189.3 (12.3)	169.2 (6.4)	0.2	181.5 (8.5)	168.7 (6.6)	0.3	199.0 (14.5)	170.7 (7.2)	0.2
$\dot{V}E$ (litres)	3.4 (0.2)	3.7 (0.2)	0.4	3.6 (0.2)	3.3 (0.1)	0.4	3.6 (0.2)	3.3 (0.1)	0.2	4.1 (0.3)	3.4 (0.2)	0.2
Resistance (cm H_2O/l·s)	18.6 (1.0)	17.4 (1.1)	0.5	26.5 (1.4)	20.1 (1.8)	0.02	26.1 (1.5)	21.8 (2.0)	0.1	24.5 (1.7)	25.0 (1.2)	0.8
Compliance (ml/cm H_2O)	17.3 (0.9)	20.3 (1.3)	0.2	11.9 (0.7)	15.8 (2.5)	0.2	10.9 (1.0)	14.9 (2.5)	0.2	13.1 (1.2)	12.4 (0.6)	0.7
Cardiac output	2.2 (0.2)	2.1 (0.2)	0.5	1.8 (0.3)	1.7 (0.2)	0.7	1.3 (0.2)	1.3 (0.1)	0.9	1.5 (0.6)	1.1 (0.2)	0.5
PVR index (WU*BSA)	2.0 (0.2)	2.0 (0.4)	0.9	3.8 (0.5)	5.6 (1.7)	0.3	5.8 (1.7)	5.4 (1.0)	0.9	6.1 (1.8)	7.6 (2.3)	0.2

p Values by t test between groups. Data expressed as mean (SEM).
BE, base excess; BP, systemic blood pressure; BSA, body surface area; Hb, haemoglobin; LA, left atrial pressure; MAP, mean airway pressure; PA, pulmonary blood pressure; P_{CO_2}, partial pressure of carbon dioxide; PEEP, peak end expiratory pressure; PIP, peak inspiratory pressure; P_{O_2}, partial pressure of oxygen; PVR, pulmonary vascular resistance; rIPC, remote ischaemic preconditioning; SBP, systolic blood pressure; $\dot{V}E$, minute ventilation; $\dot{V}O_2$, oxygen consumption; V_T, tidal volume; WU, Wood units.

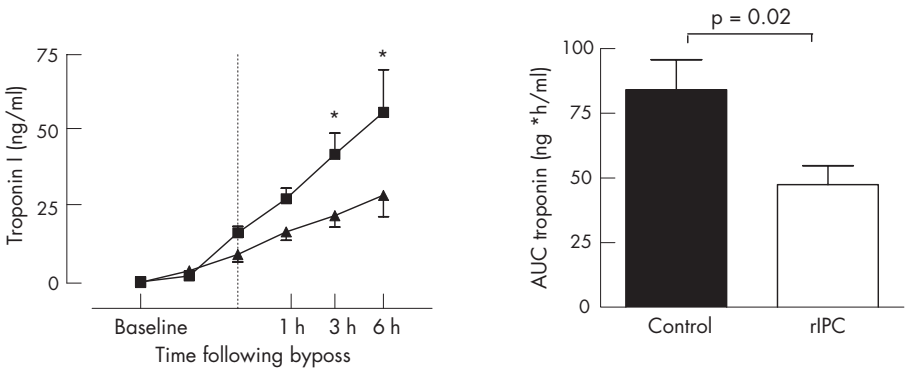

Figure 1 (Left) Troponin I at baseline and 1, 3 and 6 h after cardiopulmonary bypass in the control (■) and remote ischaemic preconditioning groups (rIPC) (▲). *p = 0.03. Dotted line denotes end of bypass and data point after baseline denotes release of aortic cross clamp. (Right) Area under the curve (AUC) analysis of troponin release showing control (black bar) and rIPC groups (open bar). p Value by unpaired t test.

support, which was administered according to prespecified parameters (see Methods). Mean dopamine doses at 1, 3 and 6 h were 2.9, 4.8 and 4.8 μg/kg/min, respectively, in the control group and 0, 2.2 and 2.0 μg/kg/min, respectively, in the rIPC group. Haemodynamic variables over the follow-up period did not differ between groups (table 1).

Biochemical indices

Troponin I release

Troponin I increased significantly at the end of CPB in both groups (fig 1). During the 6 h reperfusion period, troponin concentrations increased progressively. The increase in troponin over time was significantly lower in the rIPC group ($p = 0.02$, analysis of variance). There was no interaction with time. Furthermore, the rIPC group had significantly lower absolute concentrations than the control group at 1 and 3 h after reperfusion (16.8 (2.7) and 27.8 (3.5) ng/ml at 1 h, and 22.2 (3.8) and 42.4 (6.9) ng/ml at 3 h, respectively, both $p = 0.03$). Analysis of area under the curve also confirmed lower troponin I release in the rIPC group than in controls (57.3 (7.3) *v* 89.0 (11.6) ng·h/ml, $p = 0.02$).

Protein S-100B release

S-100B did not increase at the end of CPB compared with baseline in either group and the groups did not differ in the reperfusion period. In controls, S-100B increased from 1.0 (0.2) to a peak of 1.4 (0.2) at 1 h reperfusion ($p = 0.05$) and remained at 0.7 (0.1) in the rIPC group.

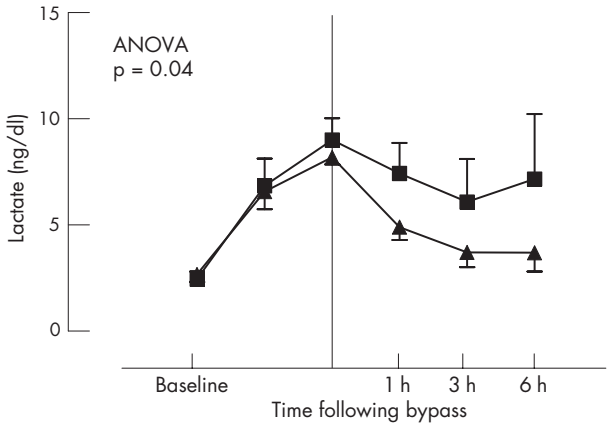

Figure 2 Lactate concentrations at baseline and 1, 3 and 6 h after cardiopulmonary bypass in the control (■) and remote ischaemic preconditioning groups (▲). p Value by analysis of variance (ANOVA). Dotted line denotes end of bypass and data point after baseline denotes release of aortic cross clamp.

Lactate release

Lactate concentrations increased after release of the aortic cross clamp and at the end of CPB but there was no difference between the groups (fig 2). During the reperfusion period, lactate concentrations dropped progressively, but the rIPC group had significantly lower concentrations than the control group over the time course ($p = 0.04$, analysis of variance). There were no significant differences at specific time points.

Ventricular function

Baseline cardiac output did not differ between groups. Analysis of load-independent indices of end systolic and end diastolic pressure–volume relationships showed a progressive increase in both groups after CPB. Systolic indices did not differ significantly between groups ($p = 0.22$, analysis of variance) over the time course, although the diastolic indices showed a trend to difference ($p = 0.06$, analysis of variance).

Lung mechanics and pulmonary vascular resistance

Lung mechanics

Pulmonary resistance rose and pulmonary compliance fell over the 3 h after CPB. However, the change in pulmonary resistance was significantly lower in the rIPC group than in the controls over the time course ($p = 0.03$, analysis of variance) (fig 3) and absolute resistance at 1 h of reperfusion was lower in the rIPC group than in controls ($p = 0.02$, unpaired t test) (table 1). The change in pulmonary compliance showed a trend to reduced compliance in the rIPC group compared with the control group over time ($p = 0.07$, analysis of variance) (fig 3). These superior indices of mechanical function in the rIPC group translated into reduced pulmonary ventilation pressures during follow up ($p = 0.001$, analysis of variance) (fig 3) and reduced absolute pressures at 1 and 3 h ($p = 0.001$ and $p = 0.002$, unpaired t test) (table 1).

Pulmonary vascular resistance

PVR increased progressively in both groups after CPB. Mean PVR at baseline and 1, 3 and 6 h was 2.0 (0.2), 3.8 (0.5), 5.8 (1.7) and 6.1 (1.8) WU/m^2 in the control group and 2.0 (0.2), 5.6 (1.7), 5.4 (1.0) and 7.6 (2.3) WU/m^2 in the rIPC group. There was no difference between groups ($p = 0.7$, analysis of variance).

DISCUSSION

This study shows that a brief period of limb ischaemia induces an rIPC stimulus that is powerful enough to attenuate cardiac injury and pulmonary dysfunction in a clinically relevant model of IR and CPB.

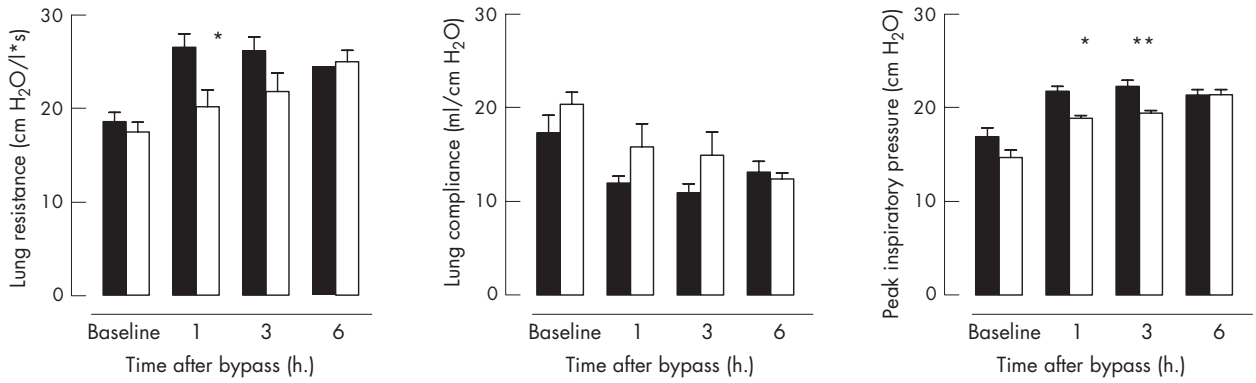

Figure 3 Pulmonary resistance (left), compliance (middle) and peak pulmonary inspiratory pressure (right) before and 1, 3 and 6 h after cardiopulmonary bypass in the control (black bars) and remote ischaemic preconditioning groups (open bars). Resistance is significantly lower at 1 h (*p = 0.02, unpaired t test) and peak inspiratory pressure significantly lower at 1 and 3 h (*p = 0.002 and **p = 0.001 by unpaired t test) in the remote preconditioning group than in controls.

The beneficial effects of rIPC on myocardial IR injury are in keeping with our previous study of rIPC, in which we showed that lower limb skeletal muscle ischaemic preconditioning reduced myocardial infarction by about 50%.[4] However, the current study is the first to show benefit of remote IPC on the acute, global IR injury associated with aortic cross clamping, and the later dysfunction that is well known to occur during the first hours after CPB.[8] None of the preconditioned animals required inotropic support to aid weaning from bypass (despite imposition of a very aggressive IR injury), and their subsequent need for inotropic support was lower. Consistent with these findings, there was a highly significant reduction in troponin I release.

Although classic preconditioning (requiring direct myocardial ischaemia) has been shown to have similar protective effects in animal models and human studies of cardiac surgical injury, it has not gained universal acceptance as a clinical tool.[3] This may, in part, be related to the demonstrable myocardial injury that may occur during such a local preconditioning stimulus but also relates to the practical difficulties associated with local induction of cardiac ischaemia in potentially unstable patients immediately before CPB.[9] The use of an rIPC stimulus clearly obviates such concerns and appears to provide a similar level of protection. A major additional advantage of rIPC is its ability to induce more widespread protective effects. Our data show that this simple manoeuvre provides additional protection against lung and possibly other tissue injury.

Although the bronchial arterial supply is maintained, pulmonary arterial blood flow is arrested during the entire period of CPB. Thus, the pulmonary endothelium and adjacent parenchymal tissues often receive the most prolonged ischaemic insult of any organ during cardiac operations. As a result, pulmonary endothelial dysfunction and abnormal respiratory mechanics are predictable sequels of CPB.[10 11] Postoperative lung mechanics were significantly improved by rIPC. Although the evolution of lung injury after CPB is clearly multifactorial, substantial evidence implicates neutrophil activation, sequestration and the release of proinflammatory cytokines and free radicals in this process.[11] Indeed, the lungs rapidly sequester activated neutrophils as part of any systemic inflammatory response.[12] While their results are not directly applicable to bypass-related injury, Harkin and co-workers,[13] who used a similar lower limb preconditioning protocol to that described in this study, reported reduced pulmonary neutrophil sequestration and improved indices of acute lung injury in response to lower limb IR injury in a porcine model. We did not quantify neutrophil responses in the current study and cannot comment on potential mechanisms. Nonetheless, rIPC afforded significant protection against adverse changes in airway resistance and compliance. This may be clinically relevant if it is demonstrable in subsequent clinical studies.

Lactate release by tissues is a manifestation of direct ischaemia or failure of cellular oxygen utilisation. Plasma lactate was consistently higher in the control group throughout the hours of postoperative monitoring. Raised serum lactate has important prognostic implications after cardiac surgery. In neonates, raised serum lactate predicts death or the requirement for extracorporeal support after congenital heart surgery and, in adults undergoing CPB requiring intra-aortic balloon pump support, blood lactate rise is associated with postoperative mortality.[14 15]

The exact mechanisms of rIPC remain unclear, but humoral and neurogenic pathways have been implicated.[16] Furthermore, the exact timing and nature of the stimulus needed to maximise protection have not been well defined. We have recently shown that the preconditioning stimulus of transient intermittent upper limb ischaemia induces pronounced changes in circulating neutrophil gene expression in humans at 24 h (second window) after the stimulus is delivered.[17] It is tempting to speculate that these changes have implications for inducing protection, and perhaps delivering the stimulus 24 h earlier would have been even more effective. These different techniques perhaps induce differential protection through varied mechanisms, and understanding the nature of the stimulus remains essential to harness the potential therapeutic value of this technique.

Study limitations

This is an experimental study of CPB. As with all such experimental animal models, these are healthy animals. Furthermore, the limited numbers in each group and investigation of multiple variables reduce the power of this study and increase the possibility of a type 1 error. However, we made several observations that are consistent and support the hypothesis that rIPC affords protection against injury induced by CPB.

In summary, this study extends our previous experimental observations into a preclinical model and confirms that rIPC achieves multisystem protection against IR and CPB-related injury. rIPC is an easily performed and clinically applicable stimulus of endogenous mechanisms of protection at the time of cardiac surgery. The underlying mechanisms of this intriguing phenomenon remain unclear and require further investigation. Nevertheless, our data should provide support

for further human studies of limb ischaemia to induce a systemic preconditioned state.

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IMAGES IN CARDIOLOGY

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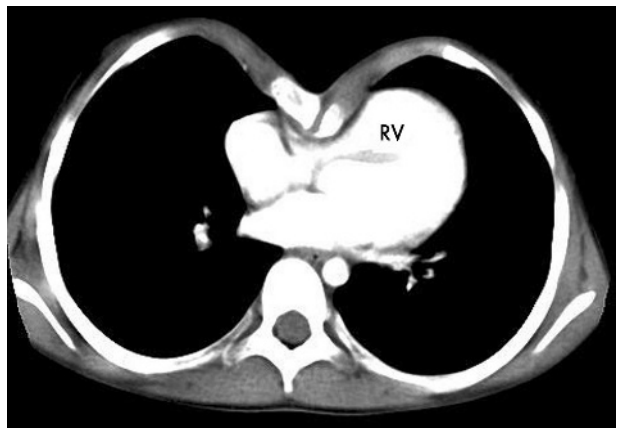
Malignant pectus excavatum

A 7-year-old girl with anterior Raphe syndrome was seen for recurrent syncope (six episodes over six months). She had undergone sternal repair of a midline defect at 3 years of age. The majority of episodes occurred in the morning and were usually associated with showering. Of concern was that an episode had occurred while swimming, requiring her to be rescued from the pool. Excepting obvious pectus excavatum, her clinical examination was normal. Her ECG, 24 ambulatory ECG and exercise test were normal and there was no evidence of long QT syndrome. Her transthoracic echocardiogram showed a structurally and functionally normal heart but the sternum appeared to compress the right ventricle. There was no flow acceleration across the inflow of the right ventricle. Syncope continued despite fluid and salt loading. A chest computed tomographic (CT) scan showed significant right ventricular compression by the sternal deformity (see panel). In the absence of any other cause for her symptoms we undertook sternochondroplasty with a resulting notable improvement in her pectus excavatum. She remains well and has had no further episodes of syncope at two years of follow up from her surgery.

Pectus excavatum is usually a cosmetic deformity but symptomatic cases of compression of the thoracic vessels and heart are described. To our knowledge this is a unique case presenting with syncope, which was presumably due to the flow limitation caused by the fixed right ventricular compression.



Chest computed tomographic scan with contrast showing right ventricular (RV) compression by the pectus excavatum.

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